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Intramolecular 1,3-Dipolar Cycloaddition at the Periphery of Heterocyclic Systems. Part 2.[1] A Mechanistic Proposal for the Facile Oxime-Nitrone Isomerization at the Periphery of Pyridine and Pyrido[1,2-*a*]pyrimidine Systems

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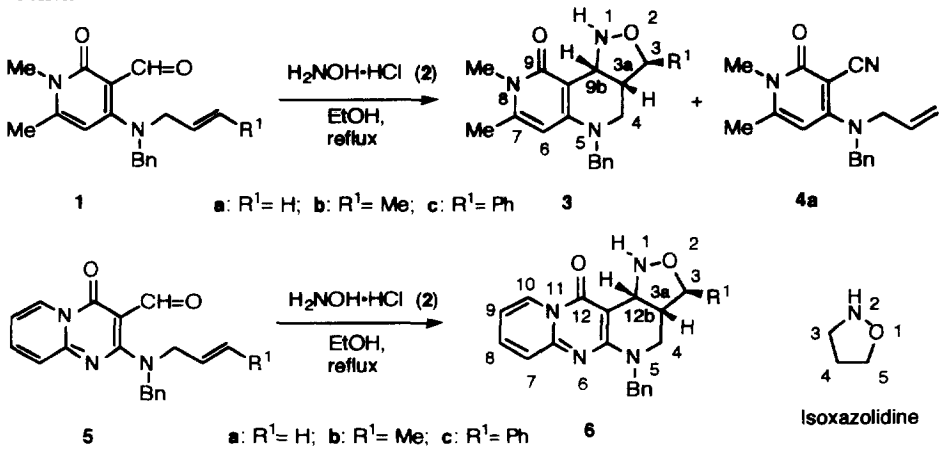
Abtract: The oximes of 4-(alk-2-enylamino)-1,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbaldehydes and 2-(alk-2-enylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehydes underwent the thermally induced 1,3-dipolar cycloadditions leading to fused isoxazolidine derivatives under very mild conditions. For the facile oxime-nitrone isomerization, we proposed a mechanistic feature that the alkenylamino nitrogen and/or carbonyl groups in the oximes could play a role as intramolecular catalyst for the consecutive proton transfers on the basis of the thermal behaviors as well as kinetic studies of the oximes isolated.

In a previous paper, we reported a facile oxime-nitrone isomerization at the periphery of pyran and 1-benzopyran; 4-(alk-2-enylamino)-2-oxo-2*H*-1-benzopyran-3-carbaldehyde oximes underwent thermally induced 1,3-dipolar cycloaddition reaction giving isoxazolo[3,4-*d*][1]benzopyrano[4,3-*b*]pyridine derivatives in good yields.[1] Although the isomerization of oxime to nitrone through the 1,2-proton transfer was theoretically regarded as an unfavorable path,[2] the isolated oximes in our case could be converted to the cycloadducts under very mild conditions. Therefore, we proposed that the alkenylamino nitrogen and/or carbonyl groups in the oximes could play a role as intramolecular catalyst in the isomerization of oxime to nitrone. However, the details of the oxime-nitrone isomerization in pyran and 1-benzopyran systems have been obscure because of the sensitivity of the heterocyclic systems toward nucleophilic conditions;[3] thermal reaction of 4-(*N*-allylbenzylamino)-2-oxo-2*H*-1-benzopyran-3-carbaldehyde oxime in aprotic solvents such as benzene and dioxane gave two isomeric 1,3-dipolar cycloadducts along with a trace amount of *N*-oxide in moderate total yields. In order to obtain better understandings on the reaction mechanism and to extend the scopes of the oxime-nitrone isomerization to other heterocyclic systems, we examined the reaction of the aldehydes of pyridine and pyrido[1,2-*a*]pyrimidine systems with hydroxylamine, in which the similar catalytic assistance of the proton transfer is also expected. The thermal behaviors of the isolated oxime as well as the kinetic studies on their isomerization suggested that the facile oxime-nitrone isomerization in these systems was attributed to the favorable proton transfer of the protonated alkenylamino and/or carbonyl moieties to the lone pair of the imine nitrogen giving the nitrone intermediates.

The Oxime-nitrone Isomerization at the Periphery of Pyridine and Pyrido[1,2-*a*]pyrimidine Systems

The reaction of 4-(*N*-allylbenzylamino)-1,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbaldehyde (**1a**) with hydroxylamine hydrochloride (**2**; 1.5 equiv.) in ethanol (EtOH) under reflux for 20 h followed by neutralization with 5% aqueous sodium hydrogen carbonate (Method A) gave the corresponding cycloadduct **3a** and 3-carbonitrile derivative **4a** in 33 and 29% yields, respectively. The reaction of aldehyde **1a** with **2** (1.5 equiv.) in refluxing EtOH in the presence of triethylamine (2.0 equiv.) gave only the cycloadduct **3a** in 88% yield (Method B). The similar reaction of 4-[*N*-benzyl(*trans*-but-2-enyl)amino]- (**1b**) and 4-[*N*-benzyl(*trans*-cinnamyl)amino]-1,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbaldehyde (**1c**) with hydroxylamine

Scheme 1.



Method A: i) **2**, EtOH, reflux; ii) 5% aq. $NaHCO_3$; iii) extracted with CH_2Cl_2; iv) SiO_2 column separation
Method B: i) **2**, Et_3N, EtOH, reflux; ii) extracted with CH_2Cl_2; iii) SiO_2 column separation

Table 1. Reaction of Aldehydes **1** and **5** with Hydroxylamine Hydrochloride (**2**) in Refluxing Solvents Leading to Fused Isoxazolidine Derivatives **3** and **6**.

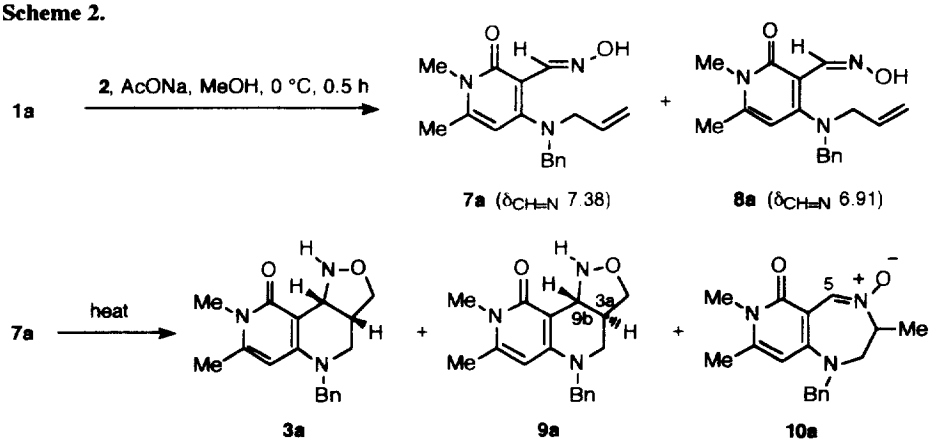
Entry	Aldehyde	R^1	Solvent	Method	Time/h	Products/%[a]
1	**1a**	H	EtOH	A	20	**3a**/33 **4a**/29
2	**1a**	H	EtOH	B	5	**3a**/88
3	**1b**	Me	EtOH	B	3	**3b**/82
4	**1c**	Ph	EtOH	A	24	**3c**/63
5	**1c**	Ph	EtOH	B	1	**3c**/63
6	**5a**	H	EtOH	A	28	**6a**/81
7	**5a**	H	EtOH	B	2	**6a**/97
8	**5a**	H	benzene	B	48	**6a**/81
9	**5b**	Me	EtOH	A	2	**6b**/94
10	**5b**	Me	EtOH	B	1	**6b**/92
11	**5c**	Ph	EtOH	A	2	**6c**/83
12	**5c**	Ph	EtOH	B	2	**6c**/95
13	**5c**	Ph	benzene	B	28	**6c**/90

[a] Isolated yield.

hydrochloride (**2**) and triethylamine in EtOH gave cycloadducts **3b** and **3c** in good yields. The aldehydes of pyrido[1,2-*a*]pyrimidine system **5a-c** also reacted with **2** in refluxing EtOH or benzene under both acidic and basic conditions (Methods A and B) giving the corresponding cycloadducts **6a-c** in good to excellent yields (Scheme 1). In these entries, the Method B was superior to the Method A in order to obtain the cycloadducts. These results are summarized in Table 1. The stereochemistries of the isoxazolidine ring in the products **3** and **6** were assigned to be 3,4-*cis* (J= 6.2-6.9 Hz) and 4,5-*trans* (J= 3.3-4.8 Hz) from the coupling constants in comparison with those of the related systems reported.[1,4] These results suggested that the nitrone intermediates formed from the oximes underwent cycloaddition in an *endo*-approaching manner. More details on the intramolecular cycloaddition of the resultant nitrone will be also discussed later. In order to elucidate the features of oxime-nitrone isomerization, we examined to isolate the oximes and investigated their thermal behaviors. The

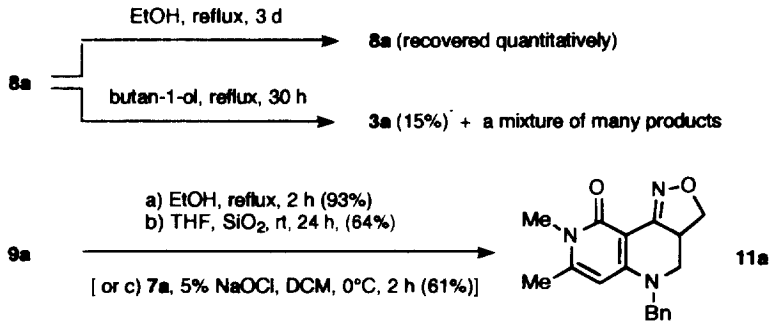
reaction of aldehyde **1a**, hydroxylamine hydrochloride (**2**; 1.2 equiv.), and sodium acetate (1.2 equiv.) in methanol (MeOH) at 0 °C for 30 min followed by crysallization and column separation gave oxime **7a** with *E*-configuration and oxime **8a** with *Z*-configuration in 45% and 7% yields, respectively. The assignment of the configurations was accomplished on the basis of the chemical shifts of imine protons accordingly to the reported ones.[5] While heating of **7a** in EtOH for 1 h gave *cis*-fused cycloadduct **3a** in 93% yield, the similar heating of **7a** in benzene for 4 h gave the cycloadduct **3a** and *trans*-fused one **9a** and *N*-oxide **10a** in good total yields. The structural confirmation of the products **9a** ($J_{3a\text{-}9b}$= 10.9 Hz) and **10a** ($\delta_{5\text{-}H}$= 8.59; $\delta_{5\text{-}C}$= 135.7) was accomplished by their spectral data in comparison with those of the related systems reported.[4, 6] The *trans*-fused cycloadduct **9a** was not very stable and converted to isoxazoline derivative **11a** during further purification procedures (Scheme 2). These reaction behaviors were consistent with those of the oximes with *E*-configuration in 1-benzopyran system.[1] The thermal behavior of oxime **8a** with *Z*-configuration was much of interest; while oxime **8a** was stable in refluxing EtOH or acetonitrile and recovered almost quantitatively, heating of **8a** in dioxane or butan-1-ol gave a mixture of many products owing to its decomposition along with the *cis*-fused cycloadduct **3a** in about 15% yield (Scheme 2). Efforts to isolate the oximes from **1b,c**, bearing more reactive dipolarophile moieties, failed; in both cases the resultant oximes underwent the thermal induced 1,3-dipolar cycloaddition giving mixtures of the oximes and cycloadducts.

Scheme 2.



Entry	Solvent	Time/h	Products/%[a]
1	EtOH	1	**3a**/93
2	benzene	4	**3a**/76 **9a**/14 **10a**/ 8

[a] Isolated yields.



The effects of the substituent of alkenylamino nitrogen on the oxime-nitrone isomerization were also examined; the reaction of aldehyde **5a** with hydroxylamine also gave oxime **12a** with *E*-configuration. Similarly, the corresponding oximes **12d-f** were obtained from 2-(*N,N*-diallylamino)- (**5d**), 2-(*N*-allylanilino)- (**5e**), and 2-[*N*-allyl(benzenesulfonyl)amino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (**5f**).

Scheme 3.

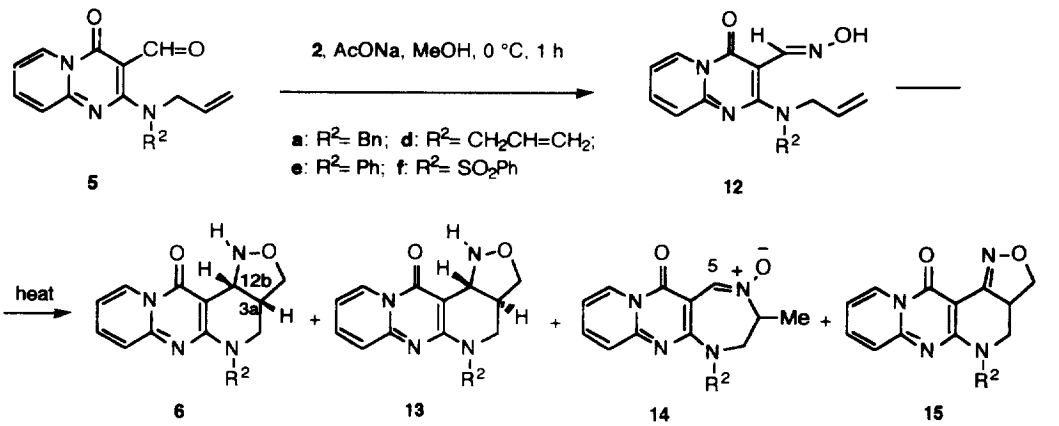


Table 2. Thermal Behaviors of the Isolated Oximes **12a** and **12d-f** in Refluxing Solvents.

Entry	Oxime	R^2	Solvent	Time/h	Products/%[a]		
1	**12a**	Bn	EtOH	2		**6a**/93	
2	**12a**	Bn	benzene	4	**6a**/76	**13a**/14	**14a**/ 8
3	**12d**	allyl	EtOH	1.5		**6d**/96	
4	**12d**	allyl	benzene	4	**6d**/70	**13d**/13	**14d**/16
5	**12d**	allyl	acetonitrile	2.5	**6d**/90	**13d**/ 7	**14d**/trace
6	**12e**	Ph	EtOH	48	**6e**/70	**15e**/ 7	
7	**12e**	Ph	benzene	96	**6e**/62	**14e**/14	**15e**/13
8	**12f**	SO_2Ph	EtOH	72	**6f**/36	unreacted **12f**/30	
9	**12f**	SO_2Ph	propan-1-ol	24	**6f**/81	unreacted **12f**/ 7	

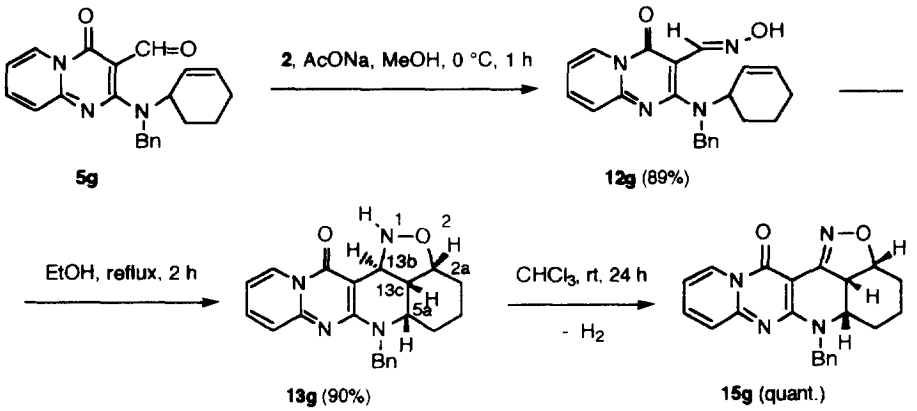
[a] Isolated yield.

Thermal behaviors of the isolated oximes **12a** and **12d-f** in several solvents were investigated; in refluxing EtOH (or propan-1-ol) the oximes **12a** and **12d-f** also gave the *cis*-fused cycloadducts **6a** and **6d-f** in good to excellent yields. The similar reaction in aprotic solvents such as benzene, toluene, and acetonitrile gave the *trans*-fused cycloadducts **13a** and **13d,e**, *N*-oxides **14**, and isoxazoline **15** together with the *cis*-fused cycloadducts **6** as the major product (Scheme 3, Table 2). The rates of the conversion decreased as the basicity of the alkenylamino nitrogen declined; in order to complete the conversion of *N*-allylanilino substrate **12e** and *N*-allyl(benzenesulfonyl)amino one **12f** into the corresponding cycloadducts **6e,f**, prolonged heating in EtOH or higher reaction temperature (in refluxing propan-1-ol) was required. The details of the effects of the allylamino substituents will be discussed later.

The similar treatment of 2-[*N*-benzyl(cyclohex-2-en-1-yl)amino]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (**5g**) with hydroxylamine gave oxime **12g** with *E*-configuration. The molecular models of the resulting nitrone intermediate from the oxime **12g** suggested that the 1,3-dipolar cycloaddition reaction in an *exo*-approaching manner was favorable to the *endo* one owing to the steric crowdedness. Heating of the oxime **12g**

in EtOH for 1.5 h gave an unstable cycloadduct **13g** in 90% yield, which was converted spontaneously into isoxazoline derivative **15g** with the elimination of hydrogen (Scheme 4).

Scheme 4.



A Mechanistic Proposal for the Oxime-Nitrone Isomerization at the Periphery of Pyrido[1,2-*a*]pyrimidine System

As mentioned above, we reported that the structural features of 4-(alk-2-enylamino)-2-oxo-2*H*-1-benzopyran-3-carbaldehyde oximes facilitated their isomerization to the corresponding nitrone intermediates, in which the alkenylamino nitrogen and/or carbonyl moieties could play as an intramolecular catalyst in the generation of nitrone intermediate.[1] In order to elucidate this point, we measured the rates of the conversion of the oximes **12a**, **12e**, and **12f** in dioxane and butan-1-ol using a HPLC method (see the Experimental section). In these conversions the rates of the disappearance of oximes were first-order with respect to the oxime concentrations. The rate constants of **12a** in dioxane at 68.8 °C were independent of its initial concentrations as expected; that at 8.97×10^{-4} M was 2.04×10^{-4} s^{-1} and that at 8.94×10^{-3} M was 2.22×10^{-4} s^{-1}. This suggests that the rate determining step in the conversion of **12** is a single-molecular process. For the conversion of oximes **12a**, **12e**, and **12f**, the relative rates at 68.8 °C and the activation parameters at the standard state (25.0 °C) are summarized in Table 3.

Table 3. Relative Rates and Activation Parameters for the Conversion of Oximes **12a**, **12e**, and **12f**.

Entry	Oxime	R^2	Solvent	Temp. (°C)	Relative Rate
1	**12a**	Bn	dioxane	68.8	45.3
2	**12e**	Ph	dioxane	68.8	2.48
3[a]	**12f**	SO_2Ph	dioxane	68.8	1.00
4	**12f**	SO_2Ph	dioxane	97.2	1.00
5	**12f**	SO_2Ph	butan-1-ol	97.2	2.05

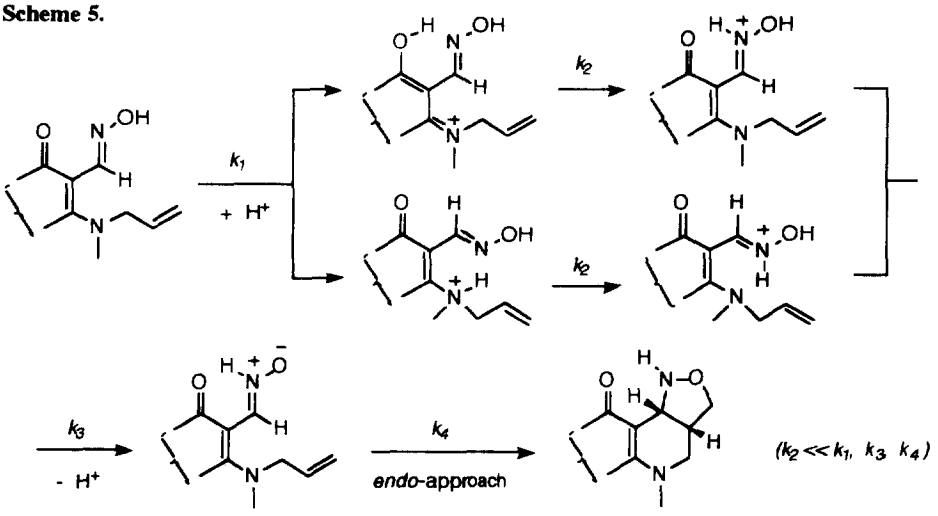
			Activation Parameters[b]		
		Solvent	$\Delta G^{\neq}$ (kcal mol^{-1})	$\Delta H^{\neq}$ (kcal mol^{-1})	$\Delta S^{\neq}$ (cal K^{-1} mol^{-1})
6	**12a**	dioxane	25.0	19.0	- 20.1
7	**12e**	dioxane	26.7	18.9	- 26.7
8	**12f**	dioxane	26.1	9.71	- 54.6
9	**12f**	butan-1-ol	28.3	23.2	- 17.0

[a] Extrapolated value. [b] At the standard state (25.0 °C).

It is clear that the basicity of the alkenylamino nitrogen in the oximes **12** effected the rates of their conversion; the oxime **12a** (R^2= Bn) underwent the thermal induced 1,3-dipolar cycloaddition reaction 45.3 times faster than the oxime **12f** (R^2= SO_2Ph). Therefore, the conversions of **12a**, **12e** and **12f** in dioxane would be classified into three categories of processes as their basicities, one of which is the expected intramolecular catalytic process in the conversion of the oxime **12a**. The other extreme is little- or non-catalytic process for **12f** and the rest is a medium-catalytic one for **12e** (R^2= Ph). It should be noted that too large negative value of the activation entropy and, in contrast, small value of the activation enthalpy in the conversion of **12f** suggests a concerted process *via* the 1,2-hydrogen shift of the oxime. Utilizing of butan-1-ol as a solvent in the conversion of **12f** at 97.2 °C accelerated 2.1 times faster than that in dioxane. The features of the activation parameters in butan-1-ol were considerably different from those in dioxane and a change in reaction process was suggested; the isomerization of the oxime **12f** to nitrone intermediate in butan-1-ol might proceed in the catalytic process.

Although the exact mechanism of the oxime-nitrone isomerization at the periphery of pyridine and pyrido[1,2-*a*]pyrimidine systems has not been accomplished, the facile generation of the nitrone intermediates was not attributed to a concerted 1,2-hydrogen shift in the oxime moiety, but two consecutive proton transfers in these systems; at first the proton in the oxime hydroxyl group transferred to the alkenylamino and/or carbonyl moieties, which was followed by the second proton transfer from the protonated amino and/or carbonyl ones to the lone pair of the imine nitrogen giving the nitrone intermediates (Scheme 5). It is not clear whether the first proton transfer is an intra- or inter-molecular process. Inspections using the molecular models of the *E*-oximes, however, suggested that the proton transfer could not take place intramolecularly owing to their geometries. This suggested that the first proton transfer would be an intermolecular process. The second one should be the rate determining and intramolecular process. In contrast to the first proton transfer process, the second one was possible only in the oximes with *E*-configuration also in geometrical reasons; both the protonated alkenylamino and carbonyl moieties could transfer the proton to the lone pair of the imine nitrogen through a seven-membered transition state. The resultant nitrone intermediates with *E*-configuration underwent the 1,3-dipolar cycloaddition reaction with the dipolarophile moiety in an *endo*-approaching manner to give the *cis*-fused isoxazolidine derivatives **3** and **6**.

Scheme 5.



Conclusion

In an early chemistry on the oxime-nitrone isomerization, Grigg and his co-worker proposed an intramolecular assistance of the proton transfers;[7] the oxime of 1,2,3-tricarbonyl compounds underwent the first

proton transfer from the oxime oxgen atom to carbonyl oxygen one *via* the thermal 1,5-shift generating a nitroso enol. Intramolecular hydrogen-bonding of the enol followed by the second proton transfer to the nitroso nitrogen generated the desired nitrone intermediate, which was allowed to react with *N*-phenylmaleimide giving the corresponding 1:1 cycloadduct. To our knowledge, further extension of this concept to other systems and the elucidation of the reaction pathway has not been found yet. Probably, our results are the second example for the facile oxime-nitrone isomerization by an intramolecular assistance, in which the proton transferred from the protonated alkenylamino and/or carbonyl moieties to the oxime nitrogen yielding the nitrone intermediate. This is supported by the findings that the oxime with *E*-configuration only underwent the facile oxime-nitrone isomerization. Finally, it should be remarked that the similar results were also obtained for the facile hydrazone-azomethine imine isomerization in these systems and that the mechanistic details of the isomerization of these oximes and hydrazones to the 1,3-dipolar tautomers will be discussed.[8]

Experimental

For general details of apparatuses and procedures, see the previous paper.[1] ^{1}H and ^{13}C NMR spectra were measured on JEOL EX-270 spectrometer (at 270 MHz for ^{1}H and 68 MHz for ^{13}C) in deuteriochloroform solution, unless otherwise stated. Overlapping splitting patterns in ^{1}H NMR spectra are indicated as ov.

Aldehydes. Aldehydes **1** and **5a-c**, **5e-f** as the starting materials were known compounds.[9] Aldehydes **5d** and **5g** were obtained from 2-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde[10] with the corresponding amines similarly to the reported method.[9]

2-(*N*,*N*-Diallylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (**5d**): yellow crystals; ^{1}H NMR δ= 4.21 (4 H, d, *J*= 5.9 Hz, C*H*$_2$CH=CH$_2$), 5.20-5.27 (4 H, ov, CH=C*H*$_2$), 5.85-6.00 (2 H, m, C*H*=CH$_2$), 6.89 (1 H, dt, *J*= 1.3, 6.9 Hz, 7-H), 7.24 (1 H, ddd, *J*= 1.0, 1.3, 8.9 Hz, 9-H), 7.66 (1 H, ddd, *J*= 1.7, 6.9, 8.9 Hz, 8-H), 8.82 (1 H, ddd, *J*= 1.0, 1.7, 6.9 Hz, 6-H), 10.17 (1 H, s, CHO).

2-[*N*-Benzyl(cyclohex-2-en-1-yl)amino]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (**5g**): pale yellow crystals; ^{1}H NMR δ= 1.61-2.21 (6 H, ov, C*H*$_2$), 4.77, 4.86 (each 1 H, each d, J= 15.2 Hz, C*H*$_2$Ph), 4.94 (1 H, m, N-C*H*<), 5.84-5.98 (2 H, ov, -C*H*=C*H*-), 6.86 (1 H, m, 7-H), 7.12-7.26 (6 H, ov, 9-H and Ph), 7.61 (1 H, ddd, *J*= 1.7, 6.9, 7.6 Hz, 8-H), 8.78 (1 H, dd, *J*= 1.7, 7.6 Hz, 6-H), 10.10 (1 H, s, CHO).

These aldehydes **5d** and **5g** were utilized for the preparation of their oximes without further purification.

Reaction of Aldehyde 1a with Hydroxylamine Hydrochloride (2) in the Presence of Triethylamine (Method B); Typical Procedures: A solution of aldehyde **1a** (0.296 g, 1.0 mmol), hydroxylamine hydrochloride (**2**; 0.100 g, 1.5 mmol), and triethylamine (0.202 g, 2.0 mmol) in EtOH (10 ml) was heated under reflux for 5 h and the solvent was evaporated. The residue was extracted with dichloromethane (DCM) (5 x 10 ml) and the combined organic layer was dried over magnesium sulfate. The DCM was evaporated to give a residue, which was subjected to column chromatography on silica gel to afford cycloadduct **3a** (0.274 g, 88%) with ethyl acetate (AcOEt)-MeOH (10:1).

(3a*R**,9b*R**)-5-Benzyl-7,8-dimethyl-1,3,3a,4,5,9b-hexahydroisoxazolo[3,4-*d*]pyrido[4,3-*b*]pyridin-9(8*H*)-one (**3a**): yellow prisms from hexane-AcOEt; mp 177-179 °C; IR (KBr) 3240 (NH), 1700 cm^{-1} (CO); ^{1}H NMR δ= 2.23 (3 H, s, 7-Me), 2.70 (3 H, m, 3a-H), 3.15 (1 H, dd, *J*= 11.0, 12.2 Hz, 4-H), 3.21 (1 H, dd, *J*= 6.2, 12.2 Hz, 4-H), 3.44 (3 H, s, 8-Me), 3.63 (1 H, dd, *J*= 2.9, 7.9 Hz, 3-H), 4.14 (1 H, dd, *J*= 7.4, 7.9 Hz, 3-H), 4.41 (1 H, d, *J*= 6.2 Hz, 9b-H), 4.54 (2 H, s, C*H*$_2$Ph), 5.3-6.3 (1 H, br, NH), 5.75 (1 H, s, 6-H), 7.17-7.38 (5 H, ov, Ph); ^{13}C NMR δ= 21.3 (7-Me), 30.3 (8-Me), 38.4 (3a-C), 48.5 (4-C), 54.1 (*C*H$_2$Ph), 54.9 (9b-C), 71.4 (3-C), 95.6 (6-C), 98.4 (9a-C), 126.5, 127.5, 128.8, 137.1 (Ph-C), 145.1 (5a-C), 151.8 (7-C), 163.8 (9-C); MS *m*/*z* 311 (M$^+$). Anal. Calcd for C$_{18}$H$_{21}$N$_3$O$_2$: C, 69.43; H, 6.80; N, 13.50%. Found: C, 69.49; H, 6.87; N, 13.56%.

4-(*N*-Allylbenzylamino)-1,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**4a**): colorless plates from hexane-benzene; mp 134-136 °C; IR (KBr) 2200 (CN), 1650 cm^{-1} (CO); ^1H NMR δ= 2.24 (3 H, s, 6-Me), 3.42 (3 H, s, 1-Me), 4.21 (2 H, d, *J*= 4.0 Hz, C*H*$_2$-CH=CH$_2$), 4.75 (2 H, s, C*H*$_2$Ph), 5.17 (1 H, dd, *J*= 1.0, 17.2 Hz, =CH*H*), 5.26 (1 H, dd, *J*= 1.0, 10.2 Hz, =C*H*H), 5.66 (1 H, s, 5-H), 5.98 (1 H, m, C*H*=CH$_2$), 7.16-7.44 (5H, ov, Ph); MS *m/z* 293 (M^+). Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.35; N, 14.33%. Found: 69.48; H, 6.87; N, 14.56%.

(3*S**,3a*R**,9b*R**)-5-Benzyl-3,7,8-trimethyl-1,3,3a,4,5,9b-hexahydroisoxazolo[3,4-*d*]pyrido[4,3-*b*]-pyridin-9(8*H*)-one (**3b**): yellow plates from hexane-benzene; mp 186-188 °C; IR (KBr) 3200 (NH), 1695 cm^{-1} (CO); ^1H NMR δ= 1.32 (3 H, d, *J*= 6.3 Hz, 3-Me), 2.22 (3 H, s, 7-Me), 2.23 (1 H, m, 3a-H), 3.12-3.26 (2 H, ov, 4-H), 3.44 (3 H, s, 8-Me), 3.87 (1 H, dq, *J*= 3.3, 6.3 Hz, 3-H), 4.48 (1 H, d, *J*= 6.6 Hz, 9b-H), 4.54, 4.57 (each 1 H, each d, *J*= 16.8 Hz, C*H*$_2$Ph), 5.72 (1 H, s, 6-H), 6.2-6.9 (1 H, br, NH), 7.17-7.38 (5 H, ov, Ph); ^{13}C NMR δ= 19.7 (3-Me), 21.4 (7-Me), 30.4 (8-Me), 45.1 (3a-C), 48.3 (4-C), 54.2 (*C*H$_2$Ph), 54.6 (9a-C), 78.7 (3-C), 95.6 (6-C), 98.2 (9a-C), 126.5, 127.5, 128.9, 137.1 (Ph-C), 145.1 (5a-C), 151.8 (7-C), 163.9 (9-C); MS *m/z* 325 (M^+). Anal. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91%. Found: C, 70.29; H, 7.08; N, 12.77%.

(3*R**,3a*R**,3b*R**)-5-Benzyl-7,8-dimethyl-3-phenyl-1,3,3a,4,5,9b-hexahydroisoxazolo[3,4-*d*]pyrido-[4,3-*b*]-pyridin-9(8*H*)-one (**3c**): yellow needles from hexane-benzene; mp 125-127 °C; IR (KBr) 3180 (NH), 1700 cm^{-1} (CO); ^1H NMR δ= 2.34 (3 H, s, 7-Me), 2.62 (1 H, m, 3a-H), 3.33-3.35 (2 H, ov, 4-H), 4.47, 4.61 (each 1 H, each d, *J*= 16.8 Hz, C*H*$_2$Ph), 4.61-4.73 (2 H, ov, 3- and 9b-H), 5.74 (1 H, s, 6-H), 7.18-7.36 (11 H, ov, NH and Ph); ^{13}C NMR δ= 21.3 (7-Me), 30.3 (8-Me), 47.3 (3a-C), 48.3 (4-C), 54.1 (*C*H$_2$Ph), 55.2 (9b-C), 84.2 (3-C), 95.6 (6-C), 98.3 (9a-C), 126.3, 126.5, 127.5, 127.9, 128.5, 128.9, 137.0, 140.5 (Ph-C), 145.2 (5a-C), 151.8 (7-C), 163.8 (9-C); MS *m/z* 387 (M^+). Anal. Calcd for $C_{24}H_{25}N_3O_2$: C, 74.39; H, 6.50; N, 10.85%. Found: C, 74.36; H, 6.56; N, 10.81%.

(3a*R**,12b*R**)-5-Benzyl-1,3,3a,4,5,12b-hexahydroisoxazolo[3',4':4,5]pyrido[2,3-*d*]pyrido[1,2-*a*]-pyrimidin-12(12*H*)-one (**6a**): colorless prisms from hexane-benzene; mp 117-119 °C; IR (KBr) 3200 (NH), 1665 cm^{-1} (CO); ^1H NMR δ= 2.73 (1 H, m, 3a-H), 3.14 (1 H, dd, *J*= 10.2, 12.8 Hz, 4-H), 3.31 (1 H, dd, *J*= 5.5, 12.8 Hz, 4-H), 3.63 (1 H, dd, *J*= 2.6, 7.7 Hz, 3-H), 4.12 (1 H, dd, *J*= 7.3, 7.7 Hz, 3-H), 4.60 (1H, d, *J*= 6.2 Hz, 12b-H), 4.91, 5.01 (each 1 H, each d, *J*= 15.2 Hz, C*H*$_2$Ph), 5.1-5.8 (1 H, br, NH), 6.87 (1 H, m, 9-H), 7.24-7.35 (6 H, ov, 7-H and Ph), 7.57 (1 H, m, 8-H), 8.89 (1 H, m, 10-H); ^{13}C NMR δ= 33.8 (3a-C), 46.2 (4-C), 51.1 (*C*H$_2$Ph), 55.3 (12b-C), 71.8 (3-C), 112.5 (12a-C), 124.2 (8-C), 127.4 (7-C), 127.5 (10-C), 127.7, 128.2, 128.6, 136.4 (Ph-C), 137.6 (8-C), 149.8 (6a-C), 157.8 (5a- and 12-C); MS *m/z* 334 (M^+). Anal. Calcd for $C_{19}H_{18}N_4O_2$: C, 68.24; H, 5.42; N, 16.76%. Found: C, 68.31; H, 5.47; N, 16.47%.

(3,*S**,3a*R**,12b*R**)-5-Benzyl-3-methyl-1,3,3a,4,5,12b-hexahydroisoxazolo[3',4':4,5]pyrido[2,3-*d*]-pyrido[1,2-*a*]pyrimidin-12(12*H*)-one (**6b**): yellow prisms from hexane-benzene; mp 155-158 °C; IR (KBr) 3200 (NH), 1660 cm^{-1} (CO); ^1H NMR (400 MHz) δ= 1.30 (3 H, d, *J*= 6.4 Hz, 3-Me), 2.29 (1 H, m, 3a-H), 3.15 (1 H, dd, *J*= 9.8, 12.7 Hz, 4-H), 3.33 (1 H, dd, *J*= 4.9, 12.7 Hz, 4-H), 3.90 (1 H, dq, *J*= 3.4, 6.4 Hz, 3-H), 4.68 (1 H, d, *J*= 6.4 Hz, 12b-H), 4.95, 5.02 (each 1 H, each d, *J*= 15.1 Hz, C*H*$_2$Ph), 5.6-6.1(1 H, br, NH), 6.88 (1 H, m, 9-H), 7.26-7.35 (6 H, ov, 7-H and Ph), 7.58 (1 H, m, 8-H), 8.90 (1H, m, 10-H); ^{13}C NMR (100 MHz) δ= 19.7 (3-Me), 45.0 (3a-C), 46.0 (4-C), 51.2 (C*H*$_2$Ph),55.1 (12b-C), 79.1 (3-C), 88.1 (12a-C), 112.6 (9-C), 124.3 (7-C), 127.5, 127.8, 128.7, 137.8 (Ph-C), 127.6 (10-C), 136.5 (8-C), 149.9 (6a-C), 157.9 (5a-C), 157.9 (12-C); MS *m/z* 348 (M^+). Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08%. Found: C, 69.01; H, 5.74; N, 16.06%.

(3*R**,3a*R**,12b*R**)-5-Benzyl-3-phenyl-1,3,3a,4,5,12b-hexahydroisoxazolo[3',4':4,5]pyrido[2,3-*d*]-pyrido[1,2-*a*]pyrimidin-12(12*H*)-one (**6c**): yellow prisms from EtOH; mp 106-109 °C; IR (KBr) 3200 (NH), 1660 cm^{-1} (CO); ^1H NMR (400 MHz) δ= 2.72 (1 H, m, 3a-H), 3.29 (1 H, m, 4-H), 3.47 (1 H, dd, *J*= 5.5, 12.8 Hz, 4-H), 4.67 (1 H, d, *J*= 4.8 Hz, 3-H), 4.85 (1 H, d, *J*= 6.6 Hz, 12b-H), 4.81, 5.20 (each 1 H, each d, *J*= 15.2 Hz, C*H*$_2$Ph), 5.8-6.6 (1 H, br, NH), 6.91 (1 H, m, 9-H), 7.26-7.36 (11 H, ov, 7-H and Ph), 7.60 (1

H, m, 8-H), 8.90 (1 H, d, *J*= 5.9 Hz, 10-H); ^{13}C NMR (100 MHz) δ= 45.7 (3a-C), 47.5 (4-C), 55.6 (*C*H$_2$Ph), 84.3 (3-C), 88.4 (12a-C), 112.7 (9-C), 124.4 (7-C), 126.2, 128.0, 128.1 x 2, 128.5, 128.7, 128.7, 137.7, 140.2 (Ph-C), 127.6 (10-C), 149.9 (6a-C), 157.7 (12-C); MS *m/z* 410 (M$^+$). Anal. Calcd for $C_{25}H_{22}N_4O_2$: C, 73.15; H, 5.40; N, 13.65%. Found: C, 72.96; H, 5.42; N, 13.43%.

Preparation of the* (E)- *and* (Z)-*Oximes from Aldehyde 1a and Hydroxylamine. A solution of aldehyde **1a** (1.2 g, 4.0 mmol), hydroxylamine hydrochloride (**2**; 0.33 g, 4.8 mmol), sodium acetate (0.39 g, 4.8 mmol) in MeOH (20 ml) was stirred at room temperature for 30 min. The solvent was evaporated at room temperature and the residue was treated with 5% aqueous sodium hydrogen carbonate and extracted with DCM (5 x 10 ml). The solvent was evaporated to dryness, which was crystallized with cold MeOH to give *(E)*-oxime **7a** (0.56 g, 45%). The filtrate was evaporated and the residue was subjected to column chromatography on silica gel to give *(Z)*-oxime **8a** (0.093 g, 7%) with chloroform-MeOH (100:1).

4-(*N*-Allylbenzylamino)-1,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbaldehyde *(E)*-oxime (**7a**): yollow crystals without recrystallization; mp 136-137 °C; IR (KBr) 3200 (OH), 1650 cm^{-1} (CO); ^{1}H NMR δ= 2.26 (3 H, s, 6-Me), 3.47 (3 H, s, 1-Me), 3.76 (2 H, d, *J*= 5.9 Hz, C*H*$_2$CH=CH$_2$), 4.38 (2 H, s, C*H*$_2$Ph), 5.13 (1 H, dd, *J*= 1.6, 16.8 Hz, =CH*H*), 5.18 (1 H, dd, *J*= 1.6, 7.9 Hz, =C*H*H), 5.76 (1 H, m, C*H*=CH$_2$), 5.84 (1 H, s, 5-H), 7.17-7.32 (5 H, ov, Ph), 8.33 (1 H, s, CH=N), 10.28 (1 H, br, OH); ^{13}C NMR δ= 21.5 (6-Me), 31.1 (1-Me), 55.1 (*C*H$_2$CH=CH$_2$), 55.7 (*C*H$_2$Ph), 101.6 (5-C), 105.2 (3-C), 118.5 (CH=*C*H$_2$), 127.3, 127.8, 128.5, 137.4 (Ph-C), 133.5 (*C*H=CH$_2$), 145.0 (4-C), 145.5 (CH=N), 158.1 (6-C), 162.2 (2-C); MS *m/z* 311 (M$^+$), 294 (M$^+$ - OH). Anal. Calcd for $C_{18}H_{21}N_3O_2$•1/2 H_2O: C, 67.48; H, 6.92; N, 13.12%. Found: C, 67.23; H, 6.81; N, 12.83%.

4-(*N*-Allylbenzylamino)-1,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbaldehyde *(Z)*-oxime (**8a**): yellow plates from hexane-benzene; mp 128-129 °C; IR (KBr) 3140 (OH), 1620 cm^{-1} (CO); ^{1}H NMR δ= 2.34 (3 H, s, 6-Me), 3.53 (3 H, s, 1-Me), 3.87 (2 H, d, *J*= 5.6 Hz, C*H*$_2$-CH=CH$_2$), 5.17 (1 H, d, *J*= 17.2 Hz, =CH*H*), 5.26 (1 H, d, *J*= 10.2 Hz, =C*H*H), 5.79 (1 H, m, C*H*=CH$_2$), 5.98 (1 H, s, 5-H), 7.15-7.35 (5 H, ov, Ph), 7.65 (1 H, s, CH=N), 11.34 (1 H, br, OH); ^{13}C NMR δ= 21.4 (6-Me), 31.5 (1-Me), 54.8 (*C*H$_2$CH=CH$_2$), 55.2 (*C*H$_2$Ph), 102.1 (5-C), 103.3 (3-C), 118.8 (=*C*H$_2$), 127.3, 127.6, 128.8, 136.5 (Ph-C), 133.0 (*C*H=CH$_2$), 147.4 (4-C), 160.0 (6-C), 162.7 (2-C); MS *m/z* 311 (M$^+$), 294 (M$^+$ - OH). Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.50%. Found: C, 69.65; H, 6.85; N, 13.42%.

Thermal Reaction of Oximes 7a and 8a; Typical Procedures: A solution of *(E)*-oxime **7a** (0.156 g, 0.5 mmol) in benzene (5 ml) was deoxygenated by introducing argon for 1 h, heated under reflux for 4 h, and the solvent was evaporated. The residue was subjected to column chromatography on silica gel to give *cis*-cycloadduct **3a** (0.118 g, 76%) with AcOEt-MeOH (10:1), *trans*-cycloadduct **9a** (0.022 g, 14%) with AcOEt-MeOH (5:1), and *N*-oxide **10a** (0.013 g, 8%) with AcOEt-MeOH (2:1), respectively.

(3a*S**,9b*R**)-5-Benzyl-7,8-dimethyl-1,3,3a,4,5,9b-hexahydroisoxazolo[3,4-*d*]pyrido[4,3-*b*]pyridin-9(8*H*)-one (**9a**): this compound was obtained as yellow crystals. However, the analytical sample for **9a** could not be accomplished because of its instability. The structure of **9a** was deduced to be the *trans*-fused isoxazolidine from the ^{1}H NMR spectral data; δ= 2.20 (3 H, s, 7-Me), 2.71 (1 H, m, 3a-H), 3.39 (3 H, s, 8-Me), 3.45-3.51 (2 H, ov, 4-H), 3.60 (1 H, dd, *J*= 6.6, 10.9 Hz, 3-H), 4.05 (1 H, d, *J*= 10.9 Hz, 9b-H), 4.15 (1 H, t, *J*= 6.6 Hz, 3-H), 4.2-4.6 (1 H, br, NH), 4.35, 4.60 (each 1 H, each d, *J*= 17.5 Hz, C*H*$_2$Ph), 5.66 (1 H, s, 6-H), 7.17-7.39 (5 H, ov, Ph).

1-Benzyl-3,7,8-trimethyl-6-oxo-1,2,5,7-tetrahydro-1*H*-pyrido[4,3-*e*][1,4]diazepine 4-oxide (**10a**): yellow prisms from EtOH; mp 242-243 °C: IR (KBr) 1625 cm^{-1}; ^{1}H NMR δ= 1.51 (1 H, d, *J*= 6.6 Hz, 3-Me), 3.23 (3 H, s, 8-Me), 3.45 (3 H, s, 7-Me), 3.55 (1 H, dd, *J*= 4.9, 14.8 Hz, 2-H), 3.63 (1 H, t, *J*= 14.8 Hz, 2-H), 4.41 (1 H, m, 3-H), 4.45, 4.93 (each 3 H, each d, *J*= 17.5 Hz, C*H*$_2$Ph), 5.67 (1 H, s, 9-H), 7.14-7.43 (5 H, ov, Ph), 8.59 (1 H, s, 5-H); ^{13}C NMR δ= 15.8 (3-Me), 21.5 (8-Me), 31.3 (7-Me), 54.2 (*C*H$_2$Ph), 57.4 (2-C), 68.9 (3-C), 97.0 (9-C), 97.1 (5a-C), 126.1, 127.9, 129.1, 135.6 (Ph-C), 135.7 (5-C), 146.0 (9a-C), 153.7

(8-C), 162.4 (6-C); MS *m/z* 311 (M^+), 265 (M^+ - O). Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.50%. Found: C, 69.44, H, 6.88; N, 13.20%.

Conversion of* trans-*Cycloadduct 9a to Isoxazoline 11a. a) A solution of cycloadduct **9a** (0.040 g, 0.13 mmol) in EtOH (2 ml) was refluxed for 2 h under open air and the reaction mixture was cooled by an ice-salt bath. The resulting crystals was collected by filtration to give isoxazoline **11a** (0.037 g, 93%); b) To a solution of **9a** (0.033 g, 0.11 mmol) in THF (5 ml) added silica gel (2.0 g) and the mixture was stirred vigorously at room temperature for 24 hr under open air. The silica gel was filtered off and washed with THF (3 x 10 ml). The combined filtrate was evaporated and the residue was crystallized with cold MeOH to give isoxazoline **11a** (0.021 g, 64%); c) The authentic sample of **11a** was obtained in 61% yield by the treatment of oxime **7a** with 5% sodium hypochlorite similarly to the reported procedure.[1]

5-Benzyl-7,8-dimethyl-3,3a,4,5-tetrahydroisoxazolo[3,4-*d*]pyrido[4,3-*b*]pyridin-9(8*H*)-one (**11a**): yellow plates from EtOH; mp 237-240 °C; IR (KBr) 1660 cm^{-1} (CO); ^1H NMR δ= 2.25 (3 H, s, 7-Me), 3.46 (3 H, s, 8-Me), 3.50-3.64 (2 H, ov, 4-H), 3.70-3.93 (2 H, ov, 3a- and 3-H), 4.50 (1 H, t, *J*= 8.2 Hz 3-H), 4.57 (2 H, s, C*H*$_2$Ph), 5.67 (1 H, s, 6-H), 7.16-7.39 (5 H, ov, Ph); ^{13}C NMR δ= 21.7 (7-Me), 30.3 (8-Me), 46.8 (3a-C), 52.2 (4-C), 54.6 (*C*H$_2$Ph), 70.2 (3-C), 92.9 (9a-C), 94.8 (6-C), 126.2, 127.7, 128.9, 136.1 (Ph-C), 148.1 (5a-C), 152.0 (9b-C), 152.9 (7-C), 159.4 (9-C). Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58%. Found: C, 69.71; H, 6.24; N, 13.52%.

Preparation of* (E)-*Oximes 12 of the Pyrido[1,2-a]pyrimidine-3-carbaldehydes 5; Typical Procedures: A solution of aldehyde **5a** (0.798 g, 2.5 mmol), hydroxylamine hydrochloride (**2**; 0.26 g, 3.7 mmol), and sodium acetate (0.34 g, 4.2 mmol) in MeOH (30 ml) was stirred at room temperature for 1 h and the solvent was evaporated. The residue was treated with 5% aqueous sodiun hydrogen carbonate and extracted with DCM (5 x 10 ml) and the solvent was evaporated to dryness, which was crystallized with cold MeOH to give *(E)*-oxime **12a** (0.687 g, 82%).

2-(*N*-Allylbenzylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde *(E)*-oxime (**12a**): yellow crystals without recrystallization; mp 127-129 °C; IR (KBr) 3220 (OH), 1660 cm^{-1} (CO); ^1H NMR = 4.09 (2 H, d, *J*= 5.9 Hz, C*H*$_2$-CH=CH$_2$), 4.82 (2 H, s, C*H*$_2$Ph), 5.19 (1 H, dd, *J*= 1.3, 13.8 Hz, =CH*H*), 5.24 (1 H, dd, *J*= 1.3, 6.9 Hz, =C*H*H), 5.88 (1 H, m, -C*H*=CH$_2$), 6.92 (1 H, m, 7-H), 7.21-7.33 (6 H, ov, 9-H and Ph), 7.62 (1 H, dd, *J*= 6.9, 8.3 Hz, 8-H), 8.28 (1 H, s, CH=N), 8.95 (1H, d, *J*= 6.9 Hz, 6-H), 10.14 (1 H, br s, OH); ^{13}C NMR δ= 52.5 (*C*H$_2$Ph), 53.3 (*C*H$_2$CH=CH$_2$), 91.1 (3-C), 113.3 (7-C), 118.2 (=CH$_2$), 124.0 (9-C), 127.2, 127.8, 128.4, 137.7 (Ph-C), 128.1 (6-C), 133.6, 136.7 (*C*H=CH$_2$ and 8-C), 144.6 (CH=N), 148.9 (9a-C), 156.2 (2-C); MS *m/z* 334 (M^+). Anal. Calcd for $C_{19}H_{18}N_4O_2$: C, 68.24; H, 5.42; N, 16.76%. Found: C, 68.15; H, 5.36; N, 16.76%.

2-(*N,N*-Diallylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde *(E)*-oxime (**12d**): obtained in 52% yield; yellow crystals without recrystallization; mp 132-133 °C; IR (KBr) 3270 (OH), 1670 cm^{-1} (CO); ^1H NMR δ= 4.13 (4 H, d, *J*= 5.6 Hz, C*H*$_2$CH=CH$_2$), 5.24 (2 H, d, *J*= 11.5 Hz, =CH*H*), 5.25 (2 H, d, *J*= 17.2 Hz, =C*H*H), 5.92 (2 H, m, C*H*=CH$_2$), 6.91 (1 H, t, *J*= 6.9 Hz, 7-H), 7.31 (1 H, d, *J*= 8.9 Hz, 9-H), 7.61 (1 H, dd, *J*= 6.9, 8.9 Hz, 8-H), 8.25 (1 H, s, CH=N), 9.00 (1 H, d, *J*= 6.9 Hz, 6-H), 10.48 (1 H, br s, OH). Anal. Calcd for $C_{15}H_{16}N_4O_2$: C, 63.36; H, 5.67; N, 19.71%. Found: C, 63.10; H, 5.73; N, 19.28%.

2-(*N*-Allylanilino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde *(E)*-oxime (**12e**): obtained in 82% yield; yellow crystals without recrystallization; mp 170-172 °C; IR (KBr) 3300 (OH), 1670 cm^{-1} (CO); ^1H NMR δ= 4.72 (2 H, d, *J*= 5.6 Hz, C*H*$_2$CH=CH$_2$), 5.15 (1 H, dd, *J*= 1.0, 10.6 Hz, =CH*H*), 5.20 (1 H, dd, *J*= 1.0, 17.2 Hz, =C*H*H), 6.04 (1 H, m, C*H*=CH$_2$), 6.98 (1 H, t, *J*= 6.6 Hz, 7-H), 7.07-7.32 (5 H, ov, Ph), 7.41 (1 H, d, *J*= 8.9 Hz, 9-H), 7.66 (1 H, ddd, *J*= 1.6, 6.6, 8.9 Hz, 8-H), 7.73 (1 H, s, CH=N), 9.02 (1 H, dd, *J*= 1.6, 6.6 Hz, 6-H), 9.73 (1 H, br, OH). Anal. Calcd for $C_{15}H_{14}N_4O_2$: C, 67.48; H, 5.03; N, 17.49%. Found: C, 67.16; H, 5.02; N, 17.42%.

2-[*N*-Allyl(benzenesulfonyl)amino]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde *(E)*-oxime (**12f**): obtained almost quantitatively; pale yellow needles from EtOH; mp 187-189 °C; IR (KBr) 3230 (OH), 1690 (CO), 1340, 1160 cm^{-1} (SO_2); ^1H NMR (DMSO-d_6) δ= 4.17 (2 H, d, *J*= 6.6 Hz, $CH_2CH=CH_2$), 5,00 (1 H, dd, *J*= 1,3, 10.2 Hz, =CH*H*), 5.07 (1 H, dd, *J*= 1.3, 17.2 Hz, =C*H*H), 5.67 (1 H, m, $CH=CH_2$), 7.36-7.96 (8 H, ov, 7-, 8-, and 9-H and Ph), 9.08 (1 H, d, *J*= 6.6 Hz, 6-H), 11.22 (1 H, s, OH); ^{13}C NMR (DMSO-d_6) δ= 51.6 ($CH_2CH=CH_2$), 107.9 (3-C), 116.8 (7-C), 119.3 (=CH_2), 125.4 (9-C), 127.5 (6-C), 128.0, 128.4, 131.1, 137.8 (Ph-C), 132.9 ($CH=CH_2$), 137.6 (8-C), 143.5 (CH=N), 148.3 (9a-C), 154.6 (2-C), 155.3 (4-C). Anal. Calcd for $C_{18}H_{16}N_4O_4S$: C, 56.24; H, 4.20; N, 14.58%. Found: C, 56.01; H, 4.24; N, 14.23%.

Thermal Reaction of the Isolated* (E)-*Oximes 12; Typical Procedures: A solution of oxime **12a** (0.167 g, 0.5 mmol) in dry benzene (5 ml) was deoxygenated by introducing argon for 1 h and heated under reflux for 4 h. The solvent was evaporated to dryness, which was subjected to column chromatography on silica gel to give *cis*-cycloadduct **6a** (0.127 g, 76%) with hexane-AcOEt (1:4), *trans*-cycloadduct **13a** (0.024 g, 14%) with hexane-AcOEt (1:5), and *N*-oxide **14a** (0.013 g, 8%) with AcOEt-MeOH (5:1), respectively.

(3a*S**,9b*R**)-5-Benzyl-1,3,3a,4,5,12b-hexahydroisoxazolo[3',4':4,5]pyrido[2,3-*d*]pyrido[1,2-*a*]-pyrimidin-12(12*H*)-one (**13a**): colorless crystals without recrystallization; mp 167-169 °C; IR (KBr) NH; not detected, 1660 cm^{-1} (CO); ^1H NMR δ= 2.61 (1 H, m, 3a-H), 3.48 (1 H, t, *J*= 11.9 Hz, 4-H), 3.54-3.62 (2 H, ov, 3-H and 4-H), 4.13 (1 H, d, *J*= 11.2 Hz, 12b-H), 4.16 (1 H, dd, *J*= 6.6, 7.6 Hz, 3-H), 4.86, 5.14 (each 1 H, each d, *J*= 15.2 Hz, CH_2Ph), 6.89 (1 H, t, *J*= 6.9 Hz, 9-H), 7.27-7.37 (7 H, ov, 7-H, NH, and Ph), 7.57 (1 H, dd, *J*= 6.9, 8.6 Hz, 8-H), 8.89 (1 H, d, *J*= 6.9 Hz, 10-H); ^{13}C NMR δ= 46.5 (3a-C), 47.5 (4-C), 51.6 (CH_2Ph), 60.0 (12b-C), 68.5 (3-C), 88.8 (12a-C), 112.7 (7-C), 124.2 (7-C), 127.5, 127.6, 128.7, 137.6 (Ph-C), 127.7 (10-C), 150.2 (6a-C), 157.5 (5a- and 12-C). Anal. Calcd for $C_{19}H_{18}N_4O_2$: C, 68.24; H, 5.42; N, 16.76%. Found: C, 68.68; H, 5.37; N, 17.13%.

1-Benzyl-3-methyl-6-oxo-1,2,3,6-tetrahydropyrido[1',2':1,2]pyrimido[4,5-*e*][1,4]diazepine 4-oxide (**14a**): brown plates from benzene; mp 233-235 °C; IR (KBr) 1650 cm^{-1} (CO); ^1H NMR δ= 1.43 (3 H, d, *J*= 6.9 Hz, 3-Me), 3.61-3.66 (2 H, ov, 2-H), 4.38 (1 H, m, 3-H), 4.61, 5.63 (each 1 H, each d, *J*= 14.9 Hz, CH_2Ph), 6.94 (1 H, ddd, *J*= 1.3, 6.3, 6.6 Hz, 9-H), 7.27-7.39 (6 H, ov, 11-H and Ph), 7.64 (1 H, dd, *J*= 6.6, 8.9 Hz, 10-H), 8.49 (1 H, s, 5-H), 8.86 (1 H, d, *J*= 6.3 Hz, 8-H); ^{13}C NMR δ= 15.6 (3-Me), 51.5 (CH_2Ph), 54.5 (2-C), 68.6 (3-C), 88.5 (5a-C), 113.5 (9-C), 124.5 (11-C), 127.9, 128.0, 128.8, 137.4 (Ph-C), 128.8 (8-C), 132.9 (5-C), 136.8 (10-C), 148.4 (11a-C), 157.3 (12a- and 6-C). Anal. Calcd for $C_{19}H_{18}N_4O_2$: C, 68.24; H, 5.42; N, 16.76%. Found: C, 68.52; H, 5.49; N, 16.54%.

(3a*R**,12b*R**)-5-Allyl-1,3,3a,4,5,12b-hexahydroisoxazolo[3',4':4,5]pyrido[2,3-*d*]pyrido[1,2-*a*]-pyrimidin-12(12*H*)-one (**6d**) : pale yellow crystals from hexane-benzene; mp 158-159 °C; IR (KBr) 3200 (NH), 1670 cm^{-1} (CO); ^1H NMR δ= 2.79 (1 H, m, 3a-H), 3.19 (1 H, dd, *J*= 10.2, 12.9 Hz, 4-H), 3.35 (1 H, dd, *J*= 5.0, 12.9 Hz, 4-H), 3.74, (1 H, dd, *J*= 3.3, 8.0 Hz, 3-H), 4.00 (1 H, dd, *J*= 6.9, 8.0 Hz, 3-H), 3.9-4.6 (1 H, br, NH), 4.32, 4.43 (each 1 H, each dd, *J*= 6, 15.5 Hz, $CH_2CH=CH_2$), 4.60 (1 H, d, *J*= 6.3 Hz, 12b-H), 5.19-5.27 (2 H, ov, =CH_2), 6.88 (1 H, dt, *J*= 1.3, 6.9 Hz, 9-H), 7.28 (1 H, dd, *J*= 1.3, 8.6 Hz, 7-H), 7.59 (1 H, ddd, *J*= 1.7, 6.9, 8.6 Hz, 8-H), 8.88 (1 H, dd, *J*= 1.7, 6.9 Hz, 10-H); ^{13}C NMR δ= 38.4 (3a-C), 46.2 (4-C), 50.5 ($CH_2CH=CH_2$), 55.4 (12b-C), 71.9 (3-C), 88.4 (12a-C), 112.5 (9-C), 117.5 (=CH_2), 124.3 (7-C), 127.5 (10-C), 133.5 ($CH=CH_2$), 136.3 (8-C), 149.8 (6a-C), 157.7 (5a-C), 157.8 (12-C). Anal. Calcd for $C_{15}H_{16}N_4O_2$: C, 63.36; H, 5.67; N, 19.71%. Found: C, 63.47; H, 5.69; N, 19.47%.

(3a*S**,12b*R**)-5-Allyl-1,3,3a,4,5,12b-hexahydroisoxazolo[3',4':4,5]pyrido[2,3-*d*]pyrido[1,2-*a*]-pyrimidin-12(12*H*)-one (**13d**) : this compound was obtained as yellow crystals. However, the analytical sample for **13d** coul not be accomplished because of its instability. The structure of **13d** was deduced to be the *trans*-fused isoxazolidine from the ^1H NMR spectral data; δ= 2.60 (1 H, m, 3a-H), 3.51 (1 H, t, *J*= 11.9 Hz, 4-H), 3.60 (1 H, m, 3-H), 3.64 (1H, dd, *J*= 6.6, 11.9 Hz, 4-H), 4.11 (1 H, d, *J*= 10.6 Hz, 12b-H), 4.21-4.25 (2 H, ov, 3-H and CH*H*CH=CH_2), 4.43 (1H, dd, *J*= 5.3, 15.5 Hz, C*H*HCH=CH_2), 5.21 (1 H, dd, *J*= 1.7, 15.8 Hz,

=CH*H*), 5.22 (1 H, dd, *J*= 1.7, 10.9 Hz, =C*H*H), 5.87 (1 H, m, C*H*=CH_2), 6.87 (1 H, t, *J*= 6.9 Hz, 9-H), 7.27 (1 H, d, *J*= 8.9 Hz, 7-H), 7.56 (1 H, dd, *J*= 6.9, 8.9 Hz, 8-H), 8.87 (1 H, d, *J*= 6.9 Hz, 10-H), NH, not detected. Dehydrogenation of **13d** by heating its EtOH solution for 6 h under open air afforded isoxazoline **15d** in 72% yield, which was fully characterized. 5-Allyl-3,3a,4,5-tetrahydroisoxazolo[3',4':4,5]pyrido[2,3-*d*]pyrido[1,2-*a*]pyrimidin-12(12*H*)-one (**15d**): yellow needles from EtOH; mp 241-243 °C; IR (KBr) 1665 cm^{-1} (CO); ^1H NMR δ= 3.49 (1 H, t, *J*= 11.9 Hz, 4-H), 3.70 (1 H, *J*= 5.6, 11.9 Hz, 4-H), 3.83-3.93 (2 H, ov, 3- and 3a-H), 4.31, 4.44 (each 1 H, each dd, *J*= 6, 15.5 Hz, NC*H*$_2$CH=CH_2), 4.62 (1 H, m, 3-H), 5.19-5.33 (2 H, ov, =C*H*$_2$), 5.85 (1 H, m, C*H*=CH_2), 6.93 (1 H, t, *J*= 6.9 Hz, 9-H), 7.25 (1 H, d, *J*= 8.9 Hz, 7-H), 7.63 (1 H, dd, *J*= 6.9, 8.9 Hz, 8-H), 8.96 (1 H, d, *J*= 6.9 Hz, 10-H); ^{13}C NMR δ= 46.4 (3a-C), 49.3 (4-C), 51.2 (N*C*H$_2$CH=CH_2), 70.7 (3-C), 84.3 (12a-C), 113.3 (9-C), 117.8 (=CH_2), 124.4 (7-C), 128.4 (10-C), 133.0 (*C*H=CH_2), 137.7 (8-C), 150.8 (5a-C), 152.5 (6a-C), 153.1 (12-C), 157.8 (12b-C). Anal. Calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85%. Found: C, 63.53; H, 4.97; N, 19.63%.

1-Allyl-3-methyl-6-oxo-1,2,3,6-tetrahydropyrido[1',2':1,2]pyrimido[4,5-*e*][1,4]diazepine 4-oxide (**14d**): yellow prisms from EtOH; mp 168-171 °C; IR (KBr) 1660 cm^{-1} (CO); ^1H NMR δ= 1.52 (3 H, d, *J*= 6.9 Hz, 3-Me), 3.63-3.67 (2 H, ov, 2-H), 4.04 (1 H, dd, *J*= 6.6, 14.9 Hz, NCH*H*CH=CH_2), 4.47 (1 H, m, 3-H), 4.89 (1 H, dd, *J*= 5.3, 14.9 Hz, NC*H*HCH=CH_2), 5.21-5.31 (2 H, ov, =C*H*$_2$), 5.90 (1 H, m, C*H*=CH_2), 6.93 (1 H, t, *J*= 6.9 Hz, 9-H), 7.29 (1 H, d, *J*= 8.3 Hz, 11-H), 7.64 (1 H, dd, *J*= 6.9, 8.3 Hz, 10-H), 8.45 (1 H, s, 5-H), 8.84 (1 H, d, *J*= 6.9 Hz, 8-H); ^{13}C NMR δ= 16.1 (3-Me), 51.3 (N*C*H$_2$CH=CH_2), 54.2 (2-C), 68.6 (3-C), 88.6 (5a-C), 113.5 (9-C), 118.6 (=CH_2), 124.4 (8- and 11-C), 127.9 (*C*H=CH_2), 133.0 (5-C), 137.3 (10-C), 148.3 (11a-C), 157.0 (12a-C), 157.2 (6-C). Anal. Calcd for $C_{15}H_{16}N_4O_2$: C, 63.36; H, 5.67; N, 19.71%. Found: C, 63.70; H, 5.76; N, 19.24%.

(3a*R**,12b*R**)-5-Phenyl-1,3,3a,4,5,12b-hexahydroisoxazolo[3',4':4,5]pyrido[2,3-*d*]pyrido[1,2-*a*]-pyrimidin-12(12*H*)-one (**6e**) : yellow needles from hexane-benzene; mp 152-154 °C; IR (KBr) 3200 (NH), 1670 cm^{-1} (CO); ^1H NMR δ= 2.93 (1 H, m, 3a-H), 3.65 (2 H, ov, 4-H), 3.75 (1 H, dd, *J*= 4.6, 7.6 Hz, 3-H), 4.16 (1 H, t, *J*= 7.6 Hz, 4-H), 4.63 (1 H, d, *J*= 6.6 Hz, 12b-H), 6.81 (1 H, dt, *J*= 1.3, 6.9 Hz, 9-H), 7.08 (1 H, dd, *J*= 1.3, 8.3 Hz, 7-H), 7.14-7.47 (7 H, ov, 8-H, NH, and Ph), 8.82 (1 H, dd, *J*= 0.7, 6.9 Hz, 10-H); ^{13}C NMR δ= 39.5 (3a-C), 50.0 (4-C), 55.4 (12b-C), 71.7 (3-C), 90.9 (12a-C), 113.0 (9-C), 124.8 (7-C), 125.6, 125.8, 128.7, 140.0 (Ph-C), 127.2 (10-C), 136.1 (8-C), 149.4 (6a-C), 157.5 (5a-C), 158.2 (12-C). Anal. Calcd for $C_{18}H_{16}N_4O_2$: C, 67.48; H, 5.03; N, 17.49%. Found: C, 67.44; H, 5.12; N, 17.32%.

1-Phenyl-3-methyl-6-oxo-1,2,3,6-tetrahydropyrido[1',2':1,2]pyrimido[4,5-*e*][1,4]diazepine 4-oxide (**14e**): brown needles from benzene; mp 235-237 °C; IR (KBr) 1660 cm^{-1} (CO); ^1H NMR δ= 1.59 (3 H, d, *J*= 6.9 Hz, 3-Me), 4.10-4.14 (2 H, ov, 2-H), 4.53 (1 H, m, 3-H), 6.92 (1 H, t, *J*= 6.9 Hz, 9-H), 7.05 (1 H, d, *J*= 8.9 Hz, 11-H), 7.24-7.57 (6 H, ov, 10-H and Ph), 8.59 (1 H, s, 5-H), 8.85 (1 H, d, *J*= 6.9 Hz, 8-H); ^{13}C NMR δ= 16.3 (3-Me), 54.4 (2-C), 69.3 (3-C), 89.8 (5a-C), 113.8 (9-C), 124.9 (11-C), 126.7, 126.8, 129.2, 145.5 (Ph-C), 127.7 (8-C), 132.3 (5-C), 137.0 (10-C), 148.0 (11a-C), 157.2 (12a-C), 157.5 (6-C); MS *m/z* 320 (M^+), 304 (M^+ - O), 262. Anal. Calcd for $C_{18}H_{16}N_4O_2$: C, 67.48; H, 5.03; N, 17.49%. Found: C, 67.66; H, 5.08; N, 17.26%.

5-Phenyl-3,3a,4,5-tetrahydroisoxazolo[3',4':4,5]pyrido[2,3-*d*]pyrido[1,2-*a*]pyrimidin-12(12*H*)-one (**15e**) : yellow plates from EtOH; mp 278-279 °C; IR (KBr) 1680 cm^{-1} (CO); ^1H NMR δ= 3.90-4.24 (4 H, ov, 3-, 3a- and 4-H x 2), 4.65 (1 H, dd, *J*= 4.0, 12.5 Hz, 3-H), 6.93 (1 H, t, *J*= 6.6 Hz, 9-H), 7.12 (1 H, d, *J*= 8.6 Hz, 5-H), 7.26-7.46 (5 H, ov, Ph), 7.66 (1 H, dd, *J*= 6.6, 8.6 Hz, 8-H), 8.98 (1 H, d, *J*= 6.6 Hz, 10-H); ^{13}C NMR δ= 47.0 (3a-C), 53.4 (4-C), 70.5 (3-C), 85.4 (12a-C), 113.7 (9-C), 124.9 (7-C), 126.6, 126.7, 129.1, 144.1 (Ph-C), 128.3 (10-C), 137.6 (8-C), 150.4 (6a-C), 152.5 (5a-C), 153.5 (12-C), 157.9 (12b-C); MS *m/z* 318 (M^+). Anal. Calcd for $C_{18}H_{14}N_4O_2$: C, 67.91; H, 4.43; N, 17.60%. Found: C, 67.84; H, 4.35; N, 17.39%.

(3a*R**,12b*R**)-5-Benzensulfonyl-1,3,3a,4,5,12b-hexahydroisoxazolo[3',4':4,5]pyrido[2,3-*d*]pyrido-[1,2-*a*]pyrimidin-12(12*H*)-one (**6f**) : pale yellow needles from EtOH; mp 128-130 °C; IR (KBr) 3170 (NH), 1680 (CO), 1340, 1170 cm^{-1} (SO_2); ^1H NMR δ= 3.14 (1 H, m, 3a-H), 3.71 (1 H, dd, *J*= 9.2, 12.5 Hz, 4-H), 3.93 (1 H, dd, *J*= 3.6, 8.6 Hz, 3-H), 4.24 (1 H, dd, *J*= 7.3, 8.6 Hz, 3-H), 4.36 (1 H, dd, *J*= 4.3, 12.5 Hz, 4-H), 4.63 (1 H, *J*= 7.6 Hz, 12b-H), 7.05 (1 H, t, *J*= 6.9 Hz, 9-H), 7.38 (1 H, d, *J*= 8.9 Hz, 7-H), 7.2-7.8 (1 H, br, NH), 7.49-7.61 (3H, ov, Ph), 7.69 (1 H, dd, *J*= 6.9, 8.9 Hz, 8-H), 8.10-8.20 (2 H, ov, Ph), 8.89 (1 H, d, *J*= 6.9 Hz, 10-H); ^{13}C NMR δ= 41.3 (3a-C), 45.8 (4-C), 55.0 (12b-C), 71.9 (3-C), 97.5 (12a-C), 114.9 (9-C), 125.0 (7-C), 127.3, 128.3, 128.4, 140.7 (Ph-C), 133.2 (10-C), 137.1 (8-C), 148.5 (6a-C), 154.5 (5a-C), 158.3 (12-C). Anal. Calcd for $C_{18}H_{16}N_4O_4S$: C, 56.24; H, 4.20; N, 14.58%. Found: C, 56.11; H, 3.88; N, 14.77%.

Preparation* (E)-*Oxime* 12g *and Its Thermal Behaviors: A solution of aldehyde **5g** (1.43 g, 4.0 mmol), hydroxylamine hydrochloride (**2**; 0.41 g, 6.0 mmol), sodium acetate (0.55 g, 6.7 mmol) in MeOH (50 ml) was stirred at room temperature for 1 h. The solvent was evaporated and the residue was treated with 5% aqueous sidium hydrogen carbonate and extracted with DCM (3 x 30 ml). After distilling the DCM off, crystallization with cold MeOH afforded oxime **12g** (1.32 g, 89%). A solution of the isolated oxime **12g** (0.187 g, 0.5 mmol) in EtOH (5 ml) was deoxygenated by introducing argon and heated under reflux for 2 h. The solvent was evaporated and the residue was subjected to a short column chromatography on silica gel to give isoxazolidine **13g** (0.168 g, 90%) with AcOEt. A solution of isoxazolidine **13g** (0.080 g, 0.21 mmol) in chloroform (3 ml) was stirred at room temperature for 24 h and usual work-up gave isoxazoline **15g** (0.078 g, 98%). Isoxazolidine **13g** was gradually converted to isoxazoline **15g** even in the crystalline state.

2-[*N*-Benzyl(cyclohex-2-en-1-yl)amino]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde *(E)*-oxime (**12g**): yellow crystals without recrystallization; mp 158-160 °C; IR (KBr) 3180 (OH), 1670 cm^{-1} (CO); ^1H NMR δ= 1.63-2.01 (6 H, ov, CH_2), 4.64, 4.73 (each 1 H, each d, *J*= 15.2 Hz, CH_2Ph), 4.70 (1 H, ov, NC*H*<), 5.76, 5.94 (each 1 H, each br d, *J*= 10.2 Hz, C*H*=C*H*), 6.89 (1 H, dd, *J*= 6.6, 6.9 Hz, 7-H), 7.11-7.31 (6 H, ov, 9-H and Ph), 7.56 (1 H, dd, *J*= 6.6, 8.6 Hz, 8-H), 8.25 (1 H, s, CH=N), 8.96 (1 H, d, *J*= 6.6 Hz, 6-H), 10.41 (1 H, br s, OH). Anal. Calcd for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; H, 14.96%. Found: C, 70.26; H, 5.91; N, 14.70%.

(2a*R**,5a*S**,13b*S**,13c*R**)-6-Benzyl-13-oxo-1,2a,3,4,5,5a,6,13,13b,13c-decahydroisoxazolo[3,4,5-*de*]pyrido[1',2':1,2]pyrimido[2,3-*b*]quinoline (**13g**): pale yellow crystals without recrystallization; mp 132-135 °C; IR (KBr) 3200 (NH), 1660 cm^{-1} (CO); ^1H NMR δ= 1.12-2.15 (6 H, ov, 3-, 4-, and 5-H), 2.51 (1 H, td, *J*= 5.6, 12.8 Hz, 13c-H), 3.72 (1 H, td, *J*= 5.6, 11.2 Hz, 5a-H), 4.35 (1 H, dt, *J*= 5.6, 9.3 Hz, 2a-H), 4.47, 5.64 (each 1 H, each d, *J*= 15.5 Hz, CH_2Ph), 4.53 (1 H, d, *J*= 12.8 Hz, 13b-H), 6.86 (1 H, t, *J*= 6.9 Hz, 10-H), 7.21-7.36 (6H, ov, 8-H and Ph), 7.54 (1 H, dd, *J*= 6.9, 8.6 Hz, 9-H), 8.88 (1 H, *J*= 6.9 Hz, 11-H); ^{13}C NMR δ= 20.4, 27.7, 29.7 (3-, 4- and 5-C), 48.0, 48.9 (5a- and 13c-C), 52.8 (CH_2Ph), 55.0 (13b-C), 75.1 (2a-C), 89.4 (13a-C), 112.6 (10-C), 124.3 (8-C), 127.2 x 2, 128.6, 138.3 (Ph-C), 127.5 (11-C), 136.1 (9-C), 149.9 (7a-C), 154.6 (6a-C), 157.3 (13-C). Anal. Calcd for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; H, 14.96%. Found: C, 70.20; H, 6.01; N, 14.72%.

(2a*R**,5a*S**,13c*R**)-6-Benzyl-13-oxo-2a,3,4,5,5a,6,13,13c-octahydroisoxazolo[3,4,5-*de*]pyrido-[1',2':1,2]pyrimido[2,3-*b*]quinoline (**15g**): yellow needles from EtOH; mp 239-240 °C: ^1H NMR δ= 0.91-2.04 (6 H, ov, 3-, 4-, and 5-H), 3.63-3.71 (2 H, ov, 5a- and 13c-H), 4.23, 5.88 (each 1 H, each d, *J*= 15.5 Hz, CH_2Ph), 4.69 (1 H, m, 2a-H), 6.94 (1 H, t, *J*= 6.9 Hz, 10-H), 7.26-7.39 (6 H, ov, 8-H and Ph), 7.63 (1 H, dd, *J*= 6.9, 8.6 Hz, 9-H), 9.01 (1 H, d, *J*= 6.9 Hz, 11-H); ^{13}C NMR δ= 17.4, 25.8, 27.7 (3-, 4-, and 5-C), 48.5, 49.6 (5a- and 13c-C), 53.4 (2a-C), 54.6 (CH_2Ph), 84.1 (13a-C), 113.3 (10-C), 124.4 (8-C), 127.4 , 127.6, 128.5, 138.0 (Ph-C), 128.3 (11-C), 137.7 (9-C), 150.9 (7a-C), 151.0 (6a-C), 153.3 (13-C), 156.4 (13b-C); MS *m/z* 372 (M^+). Anal. Calcd for $C_{22}H_{20}N_4O_2$: C, 70.95; H, 5.41; N, 15.05%. Found: C, 70.70; H, 5.38; N, 14.86%.

Kinetic Studies. The apparatuses and procedures for the measurement of the conversion rates are same as those in the preceding paper.[1] To measure the rates of the disappearance of the oximes, dichlorobenzene for oximes **12a** and **12e** and anisole for oxime **12f** were utilized as internal standards, respectively. A Wakosil-II5C18HG (id 4.6 mm x 250 mm) column was used and the flow rate of the elution was 1 ml min^{-1}. The components of the elution were MeOH-H_2O (4:1) for oximes **12a** and **12e** and acetonitrile-H_2O (1:1) for oxime **12f**. All rates of conversion of **12** under several conditions (temperature, solvent, and additive) were first-order with respect to the oxime concentration. The obtained rate constants [k (s^{-1}) x 10^5] were as bellows: for **12a** in dioxane at 8.97 x 10^{-4} M, 6.98 (56.1 °C), 9.70 (61.2 °C), and 20.37 (68.8 °C); for **12e** in dioxane at 9.36 x 10^{-4} M, 1.07 (68.8 °C), 2.26 (78.3 °C), and 4.46 (87.2°C); for **12f** in dioxane at 7.81 x 10^{-4} M, 0.654 (77.1 °C), 0.789 (81.6 °C), 0.946 (87.2 °C), and 1.472 (97.2 °C); for **12f** in butan-1-ol at 7.81 x 10^{-4} M, 0.634 (80.1 °C), 1.224 (87.2 °C), and 3.020 (97.2 °C). The relative rates and the activation parameters for the conversion of oximes **12a**, **12e**, and **12f** are summarized in Table 3.

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